REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-15 are pending.

Paper and computer readable forms of the Sequence Listing are being submitted herewith in response to the Examiner's requirement. The paper and computer readable forms of the Sequence Listing do not add new matter, and their contents are the same. It is respectfully submitted that this submission complies with 37 CFR § 1.821 et seq. Otherwise, prompt notice of any defects in the Sequence Listing is earnestly solicited and additional time is requested to comply.

The first four nucleotide sequences in the Sequence Listing were obtained from an electronic database which contains entries citing Wain-Hobson et al. Cell 40:9-17, 1985. This reference was cited on pages 11-12 of the specification. SEQ ID NOS:1-3 represent the nucleotide sequences for the NEF, REV, and TAT genes respectively; SEQ ID NO:4 represents the genomic sequence of the LAI isolate of HIV and disclosed by Wain-Hobson et al. SEQ ID NOS:5-8 represent the primers shown on page 11 of the specification. The appropriate sequence identifiers have been added to pages 11-12 of the specification.

An Abstract of the Disclosure is attached.

35 U.S.C. 112 – Definiteness

Claims 1-15 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Claim 1 recites that the papilloma virus nucleotide sequences of (i)-(iii) are from bovine papilloma virus. The Examiner's attention is directed to page 8, lines 11-35, of the specification. Moreover, an "immunologically active fragment" is defined on page 9, lines 4-5, of the specification.

The typographical error in claim 5 has been corrected.

Claims 6-7 have been amended to clarify that only the active ingredients of the vaccine are recited. As noted by the Examiner and is known in the art, a pharmaceu-

tically carrier or vehicle may also be included without affecting the essential character of the invention. Example 4 shows that gold particles may be used to deliver the vaccine when the DNA vaccine is delivered with a gene gun. Therefore, the gold particles may be considered a carrier as suggested by the Examiner.

Claims 10-11 have been amended to recite an active, positive, process step.

Examples 4 to 6 demonstrate "an immunolgically effective amount" of the self-replicating vector can be used in accordance with Applicants' disclosure. Whether or not an immune response has been elicited is determinable by methods known in the art. Moreover, this limitation is well known in the art as demonstrated by the issuance of patents such as US 6,365,160.

Applicants request withdrawal of the Section 112, second paragraph, rejections because the pending claims are clear and definite.

35 U.S.C. 101 –Utility

Claims 10-11 were rejected under Section 101 because "use" claims which do not set forth step involved in the process are allegedly informal. Applicants traverse.

Withdrawal of the Section 101 rejection is requested because claims 10-11 have been amended to recite an active, positive, process step.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1-15 were rejected under Section 112, first paragraph, as allegedly not enabled by the specification. Applicants traverse.

The Examiner alleges that the specification does not reasonably enable claims directed to a "(1) vaccine for DNA immunization against HIV, (2) against combination vaccine or combination immune response against TAT, NEF, or REV." The Applicants respectfully disagree. Examples 4 to 6 of the specification demonstrate the ability of the vectors of the invention to elicit both humoral and cellular immunological responses in mice and a cellular immunological response in monkeys (i.e., to act as vaccines). In the Applicants' view, the existing general experience in the field of vaccination, including DNA vaccination, teaches that it is possible to use a combination of immunogens in a vaccine. In fact, DNA vaccination with a vector containing desired genes comprises a combination of immunogens. Accordingly, the Applicants submit that it indeed would be within the skills of a person skilled in the art to make and use a vaccine comprising a defined mixture of the vectors of the invention as recited in their claims.

The Applicants submit that the Examiner's objection regarding "(3) utilization of any and all papillomavirus types E1, E2 genes, MO, MME regions" is addressed by specifying that the claims are directed to bovine papilloma virus nucleotide sequences.

The Examiner further alleges that the specification does not reasonably provide enable claims directed to a "(4) method of preventing HIV by administering effective amount, (5) fragment of either NEF, TAT, or [REV]." Again, the Applicants respectfully disagree. The Applicants' submit that their specification and the high level of skill in the art, especially in the field of DNA vaccination, would enable the skilled person to administer an effective amount without undue experimentation. The Applicants further refer to page 9, lines 4-5, of the specification where the immunologically active fragment is defined as "a fragment capable of eliciting an immunological response in a recipient." In the field of vaccination, subunit vaccines are known as one type of vaccine, which consist of immunogenic fragments of the pathogens and such vaccines have been safely and successfully used. See, for example, NIH publication No. 98-4219 available at http://www.niaid.nih.gov/publications/vaccine/pdf/undvacc.pdf. This publication, which is available to the general public, is evidence that immunogenic fragments are available to persons skilled in the art. For example, fragments of NEF, REV, and TAT (as well as the amino acid sequences encoded by SEQ ID NOS:1-3) can be made and their

immuno-genicity confirmed by a person skilled in the art. Other HIV sequences besides LAI (as well as the locations of the NEF, REV, and TAT genes) were also known in the art.

Regarding the Examiner's remarks on page 6 of the Action that induction of an immune response is not sufficient to show protection against a deadly virus like HIV, the Applicants respectfully disagree. In the paragraph bridging pages 2 and 3 of the specification, the Applicants describe experiments performed in the simian immunodeficiency (SIV) model with an REV-deficient virus and teach that cell-mediated immune response (CMI) against SIV regulatory proteins NEF and TAT was the only immunological correlate with protection. Thus it is fully appropriate to make conclusions on the protective ability of a vaccine. Additionally, the Applicants have different and opposite post-filing experience on induction of protective response to the post-filing reference mentioned by the Examiner set forth in a co-pending patent application relating to HIV-vaccines. Similarly, the Applicants have different and opposite post-filing experience on DNA vaccines containing more than one HIV genes in a co-pending patent application.

Finally, regarding the Examiner's remarks on pages 8-9 of the Action concerning the plasmids recited in claim 5, the Applicants totally disagree with the Examiner on the need for a deposit. The description of the plamids' constructions and the maps set forth in Figures 1 to 4 fully enables the practice of the invention recited in claim 5. This representation of a plasmid is a manner of choice in both scientific publications and in the patent literature, and is fully enabling to those skilled in the art. The fact that genes of a deathly pathogen are involved does not result in unusual difficulties in constructing the plasmids carrying such genes.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be

established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a prima facie case of obviousness without some evidence that supplies the impetus to combine those teachings in the manner proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however, broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id.*

Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-15 were rejected under Section 103(a) as allegedly being unpatentable over Ustav (WO 97/24451) and Hinkula et al. (J. Virol. 71:5528-5539, 1997). Applicants traverse.

Ustav speculates that his vector might also be useful in vaccination (e.g., against viruses) and HIV is mentioned together with other pathogenic viruses. There is no evidence, however, of this effect whatsoever. Thus a reasonable expectation of success

is lacking. The reference does not describe any pBN-plasmids that comprise the NEF, REV, or TAT gene as in the present invention. It could in no way be predicted that using such plasmids would result in a cytotoxic T lymphocyte (CTL) response, which is the most effective immune response and correlates best with a favorable clinical prognosis. This favorable effect of the vectors of the present invention is presented in the examples of the specification, and especially in Example 6.

Hinkula et al. disclose an immune response elicited in mice immunized with the NEF, REV, or TAT gene inserted in other kinds of vectors. The induced immune response (i.e., protecting antibodies and cell proliferation) were demonstrated using general, rather non-specific laboratory methods (enzyme-linked immunosorbent assay and the antigen stimulated cell proliferation, respectively). In contrast, the Applicants demonstrate their induced immune response with specific assays (e.g., Western blot), which ensure that the antibody response is actually directed to the immunogen (NEF, REV, or TAT) and not to any impurity in the preparation and they were the first to demonstrate a specific cytotoxic T lymphocyte (CTL) response, which was able to specifically destroy target cells expressing the appropriate antigen. It is the CTL response that clearly correlates with a protective effect against the virus.

Even assuming arguendo that the combination of references cited by the Examiner shows that it would be obvious to try to prepare vectors resembling the vectors of the present invention, by no means is there evidence that one of ordinary skill in the art would have had a reasonable expectation of success. The ordinarily skilled artisan would not have reasonably expected that the use of pBN vectors, which express one or more of the HIV NEF, REV, and TAT genes would result in a highly specific antibody response and in a CTL response capable of destroying HIV infected cells early in the viral infection cycle, as disclosed in the present invention.

Claims 1-15 were rejected under Section 103(a) as allegedly being unpatentable over Woo et al. (WO 94/12629) in view of Hinkula et al. Applicants traverse.

The disclosure of Hinkula et al. and its deficiencies were discussed above. These deficiencies are not remedied by combination with Woo et al., which generally discloses self-replicating vectors without specific recitation of regulatory HIV genes. The vectors

contain partly similar (but not like) elements as the vectors of the present application. The Applicants submit, however, that even the knowledge of vectors disclosed by Woo et al. and the results of Hinkula et al. would not have motivated one skilled in the art, due to the complexity of the vectors, to construct vectors of the present invention, let alone with a reasonable expectation of success.

With the reference to what is set forth above, the Applicants respectfully ask the Examiner to reconsider and withdraw his Section 103 rejections because the invention as claimed would not have been obvious to a person of ordinary skill in the art at the time it was made.

Conclusion

Having fully responded to all of the pending objections and rejections contained in the Office Action (Paper No. 7), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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APPENDIX
MARKED-UP VERSION TO SHOW CHANGES

IN THE SECIFICATION

The specification is amended as follows.

Page 11, third paragraph starting at line 13:

Phase 1:

The HIV-1 REV (SEQ ID NO:2) and TAT (SEQ ID NO:3) genes from isolate BRU also called LAI (SEQ ID NO:4) (Wain-Hobson et al. Cell 40:9-17, 1985) were amplified from the pcREV and pcTAT vectors (Arya et al. Science 229:69-73, 1985) using Dynazyme Taq DNA polymerase (Finnzymes, Finland) and the following primers that have restriction enzyme sites for enzymes XhoI and XbaI:

Page 11, fourth paragraph starting at line 20:

For REV:

5′-TTTTTCTAGAACCATGGCAGGAAGAAGCGGA-3′ (SEQ ID NO:5)

5′-TTTTCTCGAGCTATTCTTTAGTTCCTGG-3′ (SEQ ID NO:6)

Page 11, fifth paragraph starting at line 24:

For TAT:

5′-TTTTTCTAGAACCATGGAGCCAGTAGATCCT-3′ (SEQ ID NO:7)

5′-TTTTCTCGAGCTAATCGAACGGATCTGC-3′ (SEQ ID NO:8)

Page 12, fourth paragraph starting at line 19:

Phase 1:

The HIV-1 NEF (SEQ ID NO:1) gene was obtained from a plasmid pcNEF vector, which contained the LAI isolate NEF gene inserted into a pcTAT vector lacking the TAT gene. The NEF gene used for further cloning was achieved as a 1.3 kb fragment by Spe I and Hind III digestion from pcNEF. To eliminate the reformation of the Hind III site on

ligation, after Hind III digestion the fragment was treated with Klenow enzyme and a mix of dATP, dCTP, dGTP nucleotides after which the Spe I digestion was performed. The fragments obtained were separated by electrophoresis on a 1% agarose gel alongside standard size markers. Bands of correct size were cut out and the DNA recovered using the Sephaglas Bandprep Kit (Pharmacia Biotech), following the manufacturer's protocol.

IN THE CLAIMS

The claims are amended as follows.

1. (Amended) A self-replicating recombinant vector comprising bovine papilloma virus nucleotide sequences consisting essentially of

(i) a bovine papilloma E1 gene and E2 gene,

(ii) a minimal origin of replication of a bovine papilloma virus,

(iii) a minichromosomal maintenance element of a bovine papilloma virus, and

a heterologous nucleotide sequence selected from the group consisting of a nucleotide sequence encoding the HIV regulatory protein NEF, a nucleotide sequence encoding the HIV regulatory protein REV, a nucleotide sequence encoding the HIV regulatory protein [or] TAT, and a nucleotide sequence encoding a [or an immunologically active] fragment thereof capable of eliciting an immunological response in a recipient.

2. (Amended) A self-replicating vector of claim 1 wherein the bovine papilloma nucleotide sequences are nucleotide sequences of bovine papilloma virus type 1 and the heterologous nucleotide sequence is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and a nucleotide sequence encoding a fragment thereof capable of eliciting an immunological response in a recipient [is bovine papilloma virus (BPV)].

3. (Amended) A self-replicating vector of claim 1 wherein the heterologous nucleotide sequence encodes the HIV-1 NEF protein (SEQ ID NO:1).

4. (Amended) A self-replicating vector of claim 1 wherein E1 is under the control of the srαL promoter [promotor] or the thymidine kinase promoter [promotor].

5. (Amended) A self-replicating vector of claim 4 which is selected from the group consisting of pBNtkREV, pBNsrαTAT, and [or] pBNsrαNEF as shown in Figures 2, 3, and [or] 4 respectively.

6. (Amended) A vaccine for DNA immunization against HIV consisting essentially of [comprising] a self-replicating vector of claim 1.

7. (Amended) A vaccine for DNA immunization against HIV consisting essentially of [claim 6 comprising] a mixture of vectors, wherein at least one of the mixture of vectors is a self-replicating vector of claim 1 [encoding different HIV regulatory proteins or immunologically active fragments thereof].

8. (Amended) A method [Method] for preparing a self-replicating recombinant vector of claim 1, said method comprising

A) inserting a heterologous nucleotide sequence encoding the HIV regulatory protein NEF, REV or TAT or an immunologically active fragment thereof into a vector comprising bovine papilloma virus nucleotide sequences consisting essentially of

(i) a bovine papilloma E1 gene and E2 gene,

(ii) a minimal origin of replication of a bovine papilloma virus, and

(iii) a minichromosomal maintenance element of a bovine papilloma virus;[, and]

B) transforming a host cell with the resulting self-replicating recombinant vector;[,]

C) culturing the host cell;[,] and

D) recovering said vector.

9. (Amended) The method of claim 8 wherein the host cell is an *E. coli* [E. coli] cell.

10. (Amended) A method of [Use of a self-replicating vector of claim 1 for the manufacture of a] DNA immunization [vaccine] against HIV comprising immunizing a person with a vaccine of claim 6 to induce a cytotoxic T lymphocyte response.

11. (Amended) A method of DNA immunization agains HIV [The use of claim 9 in the manufacture of a vaccine] comprising immunizing a person with a vaccine of claim 7 to induce a cytotoxic T lymphocyte response [a mixture of vectors encoding different HIV regulatory proteins or immunologically active fragments thereof].

12. (Amended) A method [Method of treating or preventing HIV] comprising administering to a person in need thereof an immunogically effective amount of a self-replicating vector of claim 1, and expressing the NEF, REV or TAT protein or an immunologically active fragment thereof in said person.

13. (Amended) A [The] method [of claim 12] comprising administering to a person in need thereof an immunogically effective amount of a mixture of vectors, wherein at least one of the mixture of vectors is a self-replicating vector of claim 1 [encoding different HIV regulatory proteins or immunologically active fragments thereof].

IN THE ABSTRACT

The Abstract of the Disclosure is attached.

IN THE SEQUENCE LISTING

Paper and computer readable copies of the Sequence Listing are attached.